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(54) Title: NOVEL PHARMACEUTICAL COMPOSITIONS

(57) Abstract: A dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release. Wherein the modified release active ingredient is selected from high dose, low solubility active ingredients or low dose, low solubility active ingredients or low dose, high solubility active ingredients and the immediate release active ingredient is selected from low dose active ingredients.

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NOVEL PHARMACEUTICAL COMPOSITIONS

FIELD OF INVENTION

This invention relates to a dosage form comprising of the combination of an active ingredient as modified release and an active ingredient as immediate release and the preparation of the same, wherein the modified release active ingredient is selected from high dose, low solubility active ingredients or low dose, low solubility active ingredients or low dose, high solubility active ingredients and the immediate release active ingredient is selected from low dose active ingredients.

BACKGROUND OF THE INVENTION

Combining two active ingredients in one pharmaceutical unit to improve patient compliance is known in literature. It can be either in the form of two or more active ingredients in immediate release form or a combination of immediate release and modified release form. There are various techniques by which the combination of immediate release and modified release is formulated in single dosage form.

Several examples of formulations having combination of immediate release active ingredient and modified release active ingredient are described below.

Shoichi Higo and Kazuo Igusa describes in US patent no. 5,985,843 various types of pharmaceutical formulations, which consists of a delayed release of sucralfate and an immediate release fraction of another active ingredient. The pharmaceutical dosage forms are a tablet formulation containing immediate release and delayed release granules; a two or three layer tablet; a tablet with delayed release core surrounded by immediate release shell; a delayed release tablet / granule coated with a film of immediate release active ingredient.

Similarly Jurgen Zeidler et.al describes in US patent No. 6,001,391 a process for producing solid combination tablets, which have atleast two phases. The one of the two phases is processed by melt extrusion technique and contains a water soluble or swellable binder.

A compressed V-shaped center scored double layer tablet is disclosed by George M. Krause et. al in US patent no. 3,336,200, one layer of which contains immediate release Active Ingredient and the other layer contains sustained

release Active Ingredient. The tablet is divisible in two equal halves.

Similarly Jacob A. Glassman described in US Patent No. 4,503,031 a super fast starting, slow release medicinal tablet, wherein the tablet is comprised of two layers of compressed matrix that are fused together by means of readily dissolvable adhesive substance.

Allan A. Rubin describes in US patent no. 6,238,699 B1 a pharmaceutical dosage form of carbidopa and levodopa where both the Active Ingredients are present as immediate release and sustained release. The formulation is in the form of inlay tablet or bilayered tablet or a capsule containing pellets.

Block Jurgen et. al. describes in PCT application No. WO 01/72286 A1 a formulation of vitamin composition whereas a beadlet comprises a slow release core coated by a controlled release coating. The sustained release core is coated with an immediate release layer.

Richard Ting and Charles Hscao describes in US patent No. 6,372,254 B1 a press coated, pulsatile active ingredient delivery system which comprises a core of immediate release, enveloped by an extended release compartment.

The need to use active ingredients with different and complementary mechanisms of action frequently arises in treatment of diabetes. There are several reasons to do this, namely, the disease itself is progressive, with deterioration of glycemic control over time; mono-therapeutic attempts to achieve and maintain glycemic control often fail in the long run; multiple defects in the disease and consequently primary drug failures (1,2,3).

Current guidelines for combination therapy advise the use of agents with differing and complementary mechanisms of action in order to maximize therapeutic activity and reduce toxicity. Earlier introduction of combination therapy is increasingly being recommended. The commonly combined active ingredients include biguanides (metformin) + sulphonylureas, biguanides + PPARγ agonists (thiazolidinediones), sulphonylureas + thiazolidinediones, non-sulfonylurea secretagogues (repaglinide) + biguanides etc.

Fixed dose combinations of many of the above mentioned co-administer active ingredients have also been approved by the FDA. Most of these combinations are conventional formulations combined together into a single tablet.

However, because of the disparity in the duration of action (half-life), these combinations are given twice or thrice a day.

To reduce this disparity in the duration of action, a novel strategy would be to combine a sustained release formulation of one active ingredient (shorter duration of action) with conventional formulation (long duration of action) of another active ingredient. This would make it possible to give the active ingredients in same dosing frequency.

This type of combination will give better compliance and a relative freedom from mealtime drug administration, thus, improving the quality of life. More importantly, because of prolonged duration of action, it shall produce a stricter control of blood glucose and consequently less diabetic complications.

The techniques described above are not versatile enough to formulate combination dosage form of drugs with varying solubilities and dose in which the release profiles of the two active ingredients are different.

Accordingly a need exists for a versatile dosage form providing combination of immediate release and modified release active ingredients with varying solubilities and doses. Further, the dosage form should be simple and economical to produce.

An object of the present invention is to provide a dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release, wherein the modified release active ingredient is selected from high dose, low solubility active ingredients or low dose, low solubility active ingredients or low dose, high solubility active ingredients and the immediate release active ingredient is selected from low dose active ingredients.

Further object of the present invention to provide a dosage form, which uses dual retard technique to control the release of the high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient and significantly reduce the amount of release controlling agents.

A further object of the present invention is to provide a dosage form, containing one active ingredient in an immediate release form and another active ingredient as modified release and the release or disintegration of the

immediate release active ingredient is not hindered by the modified release ingredient.

Yet another object of the present invention is to provide a dosage form, which effectively avoids the problem of separation of layers of multilayered tablets.

A further object of the present invention is a formulation, which gives accurate dosing and is prepared by novel and simple processes.

A further object of the present invention is to provide a dosage form, which can be given twice a day or more preferably can be given once a day.

Still another object of the present invention is to reduce the chances of dose dumping, unnecessary burst effects and failure of the system, which are otherwise usually associated with simple matrix or reservoir systems.

SUMMARY OF THE INVENTION

The above objects are realized by a dosage form, which is comprised of an inner portion and an outer portion. The inner portion is surrounded by the outer portion in such a manner that only one surface of the inner portion is exposed. The inner portion contains a low dose active ingredient in immediate release form and the outer portion contains a high dose, low solubility or low dose, low solubility or low dose, high solubility active ingredient as modified release.

The present invention also provides solid oral dosage form comprising a composition according to the invention.

The present invention also teaches the use of dual retard technique to effectively control the release rate of modified release active ingredient by using small quantity of release controlling agents. This dual retard technique thus sufficiently reduces the size of the dosage form, which is convenient for swallowing.

The present invention further teaches the use of hydrophobic release controlling agents, which do not hinder the release of the immediate release active ingredient.

The present invention further provides the dosage form that effectively prevents the problem of separation of the layers of the multilayered tablets.

The present invention also provides a novel process for preparing the novel formulations of the invention.

The present invention further provides a method of treating an animal, particularly a human in need of treatment utilizing the active agents, comprising administering a therapeutically effective amount of composition or solid oral dosage form according to the invention to provide administration of two active ingredients one in immediate release and other in modified release form.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a novel dosage form of combination of high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient, as modified release and low dose active ingredient as immediate release, suitable for swallowing comprising dual retard technique to control the release of the modified release active ingredient with sufficient reduction in the amount of release controlling agent, without interfering the release of each other.

The term "modified release" as used herein in relation to the composition according to the invention or a rate controlling polymer or used in any other context means release, which is not immediate release and is taken to encompass controlled release, sustained release, prolonged release, timed release, retarded release, extended release and delayed release. The term "modified release dosage form" as used herein can be described as dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products (as per US FDA guideline for 'SUPAC-MR: Modified Release Solid Oral Dosage Forms').

The term "immediate release" as used herein in relation to composition according to the invention or used in any other context means release which is not modified release and releases more than 60% of the active ingredient within 60 minutes. The term "immediate release dosage form" as used herein can be described as dosage form which allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug (as per US FDA guideline for 'SUPAC-MR: Modified Release Solid Oral Dosage Forms').

The term "dosage form" denotes any form of the formulation like tablet, capsule etc. that contains an amount

sufficient to achieve a therapeutic effect with a single administration.

The term "active ingredient" refers to an agent, active ingredient compound or other substance, or compositions and mixture thereof that provide some pharmacological, often beneficial, effect. Reference to a specific active ingredient shall include where appropriate the active ingredient and it's pharmaceutically acceptable salts.

The term "high dose" as used herein refers to the weight of active ingredient in unit dosage form according to the invention is from 500 mg to 1500 mg.

The term "low dose" as used herein for immediate release active ingredient refers to the weight of the active ingredient in unit dosage form according to the invention is less than or equal to 50 mg.

The term "low dose" as used herein for modified release active ingredient refers to the weight of the active ingredient in unit dosage form according to the invention is 0.1mg to 500 mg.

The term "high solubility" as used herein means that from less than 1 part to 30 parts of water will require dissolving 1 part of active ingredient.

The term "low solubility" as used herein relation to modified release means that more than 30 parts of solvent is required to dissolve 1 part of active ingredient.

The invention provides a novel dosage form of high dose, low solubility or low dose, low solubility or low dose high solubility active ingredient as modified release and a low dose active ingredient as immediate release.

The weight ratio of immediate release active ingredient to modified release active ingredient with high dose low solubility is from 1: 10 to 1: 15000

The weight ratio of immediate release active ingredient to modified release active ingredient with low dose is from 500: 1 to 1: 5000.

The dosage form comprises of two parts (i) inner portion as an immediate release and (ii) outer portion as modified release. The two parts are compressed together in such a way that one surface of the inner portion remains exposed and the remaining surfaces are covered by the outer portion.

(i) Inner portion- Inner portion comprises of a low dose active ingredient and includes one or more commonly used excipients in oral immediate release pharmaceutical formulations.

The low dose active ingredient for immediate release (in inner portion) can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminum salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Further, the low dose active ingredient for immediate release, where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

In the dosage form of the present invention, the inner portion may optionally contain more than one low dose active ingredient for immediate release.

In the dosage form of the present invention, the inner portion may optionally contain more than one low dose active ingredient.

The low dose active ingredient for immediate release is in the form of immediate release and has dose of 50 mg or less.

The low dose active ingredients for immediate release are comprises of the following therapeutic classes but not limited to antidiabetic agents, anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arththriics, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations,

anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors, vertigo agents, sulphonylurease, meglitinides, PPAR gamma agonist [insulin sensitisers (thiazolidinedione)], PPAR alpha and gamma agonist, alpha-glucosidase inhibitors and the active ingredients described in united states patent numbers 2968158, 3097242, 3454635, 3654357, 3668215, 3669966, 3708486, 3801495, 5104888, 5232945, 5264451, 5478852, 6296874, and European patent publication numbers EP0008203, EP0032128, EP0139421, EP0155845, EP0177353, EP0208420, EP0257881, EP0306228, EP0319189, EP0332331, EP0332332, EP0428312, EP0489663, EP0508740, EP0528734, EP0533933, EP0833933, EP87112480.6 and Japanese patent number 05271204 and United Kingdom patent numbers 5504078, GB2088365A and PCT patent application numbers WO91/19702, WO92/03425, WO92/18501, WO93/02079, WO93/21166, WO93/22445, WO94/01420, WO94/05659.

Examples of low dose active ingredients for immediate release comprises of but not limited to zafirlukast, quinapril hydrochloride, isotretinoin, rabeprazole sodium, estradiol(e2), norethindrone acetate, risedronate sodium, pioglitazone HCl, amphetamine, anagrelide hydrochloride, biperiden HCl, mephalan, alprazolam, ramipril, naratriptan hydrochloride, leflunomide, anastrozole, exemestane, paroxetine mesylate, candesartan cilexetil, almotriptan, cerivastatin, betaxolol hydrochloride, bisoprolol fumarate, deloratadine, clonazepam, clorazepate dipotassium, clozapine, methylphenidate HCl, carvedilol, warfarin sodium, norgestrel, ethinyl estradiol, cyclophosphamide, pemoline, liothyronine sodium, misoprostol, tolterodine tartrate, dextroamphetamine sulfate, dicyclomine hydrochloride, digoxin, oxybutynin chloride, doxazosin mesylate, ethacrynate sodium, venlafaxine HCl, enalapril maleate, estradiol, estropipate, famotidine, letrozole, fludrocortisone acetate, fluoxetine, dexmethylphenidate HCl, alendronate sodium, ziprasidone, glipizide, glyburide, miglitol, guanabenz acetate, haloperidol, doxercalciferol, zalcitabine, hydrochlorothiazide, hydromorphone HCl,

indapamide, estradiol, nitric oxide, ketorolac tromethamine, clonazepam, granisetron, lamotrigine, fluvastatin sodium, levonorgestrel, levothyroxine sodium, atorvastatin calcium, lisinopril, minoxidil, loperamide, loratidine, lorazepam, lovastatin, pravastatin sodium, fluvoxamine maleate, acetaminophen, acyclovir, aminocaproic acid, pitavastatin, rosuvastatin, dalvastatin, sertraline,pitavastatin,rosuvastatin,dalvastatin,escetalopr am,sertraline,celecoxib,parecoxib,valdecoxib, glibenclamide (glyburide),glipizide, gliclazide, glimepiride, tolazamide, tolbutamide, clorpropamide, gliquidone, nateglinide, glyburide, glisoxepid, glibornuride, phenbutamide, tolcyclamide, repaglinide, troglitazone, ciglitazone, pioglitazone, englitazone, acarbose, voglibose, emiglitate, miglitol, farglitazar, nebivolol, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid and L-6766892.

Further examples of low dose for immediate release, antidiabetic active ingredients comprises of but not limited to JTT-501 (PNU-182716) (Reglitazar),AR-H039242, MCC-555 (Netoglitazone), AR-H049020 , Tesaglitazar), CS-011 (CI-1037), GW-409544X, KRP-297, RG-12525, BM-15.2054, CLX-0940, CLX-0921, DRF-2189, GW-1929, GW-9820, LR-90, LY-510929, NIP-221, NIP-223, JTP-20993, LY 29311 Na, FK 614, BMS 298585, R 483, TAK 559, DRF 2725 (Ragaglitazar), L-686398, L-168049, L-805645, L-054852, Demethyl asteriquinone B1 (L-783281), L-363586, KRP-297, P32/98, CRE-16336 and EML-16257.

As indicated above the inner portion of the present invention may comprise auxiliary excipients such as for example diluents, binders, lubricants, surfactants, disintegrants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Suitable diluents include for example pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, starch, dibasic calcium phosphate, saccharides, and/or mixtures of the foregoing. Examples of diluents include microcrystalline celluloses such as those sold under the Trade Mark Avicel pH 101, Avicel pH 102, Avicel pH 112, Avicel pH 200, Avicel PH301 and Avicel pH 302; lactose such as lactose monohydrate, lactose anhydrous and Pharmatose DCL21 (Pharmatose is a Trade Mark),

including anhydrous, monohydrate and spray dried forms; dibasic calcium phosphate such as Emcompress (Emcompress is a Trade Mark); mannitol, Pearlitol SD 200 (Pearlitol SD 200 is a trade mark), starch, sorbitol, sucrose and glucose.

Suitable binders include for example starch, povidone, hydroxypropylmethylcellulose, pregelatinised starch, hydroxypropylcellulose and/or mixtures of the foregoing.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal silicon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

Suitable anti-taking agents i.e. antiadherent, are selected from the group comprising of colloidal silicon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

Suitable opacifying agent can be titanium dioxide.

Pigments can be selected from iron oxides, lake colours and dyes.

Suitable disintegrants include for example lightly crosslinked polyvinyl pyrolidone, corn starch, potato

starch, maize starch and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate and combinations and mixtures thereof.

The ranges of active ingredient and excipients for the inner portion are as follows-

Active ingredient	0.1	to 90 % w/w
Diluent(s)	10.0	to 90 % w/w
Binder	0.5	to 20 % w/w
Disintegrating agent	0.5	to 20 % w/w
Lubricant(s)/colourants	0.1	to 05 % w/w

(ii) **Outer Portion:** The outer portion comprises of a) micro matrix particles containing high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient and one or more hydrophobic release controlling agent, b) coating of Micro matrix particles with one or more hydrophobic release controlling agents. The outer portion may also include one or more commonly used excipients in oral pharmaceutical formulations. The release of the high dose, low solubility active ingredient or low dose, low

solubility active ingredient or low dose high solubility active ingredient is controlled through dual retard technique. The dual retard technique is a combination of matrix formulations and reservoir formulations. First the micro matrix particles of high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility dose active ingredient and one or more hydrophobic release controlling agents are formed and then these are further coated with one or more release controlling agents. Thus the dual retard release technique presents the double barriers and effectively controls the diffusion of the high dose, low solubility or low dose, low solubility or low dose high solubility active ingredients from the present invention in predictable manner and also significantly reduces the amount of release controlling agents. The other advantages of the present invention are such as it reduces the chances of dose dumping, unnecessary burst effects and failure of the system, which are otherwise usually associated with simple matrix or reservoir systems.

Further advantages of present invention include the disintegration of inner portion is not hindered as nonswellable release controlling agents are used which do not swell and maintain the shape during operation and it effectively prevents the separation of the layers of the multilayered tablets which is normally associated with normal multilayered tablets.

The high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient can be present in the form of a free base or in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety such as alkali metal salts like Li, Na and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzensulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Further, the high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient, where applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture of enantiomers or polymorphs thereof.

The high dose active ingredient is in the form of modified release and has dose from 500 mg to 1500 mg.

The high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredients are comprises of the following therapeutic classes but not limited to antidiabetic agents, anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritis, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors,vertigo agents, biguanides and the active ingredients described in united states patent numbers 3957853, 4080472, 3174901, 4835184, 6031004.

Examples of high dose, low solubility active ingredients comprises of but not limited to cefuroxime axetil, acetylsalicyclic acid, ibuprofen, gemfibrozil, sulfasalazine, acyclovir, cefadroxil, amoxicillin, cefaclor, ticlopidine hydrochloride, ciprofloxacin hydrochloride etc. Other drugs suitable for use and meeting the solubility and dose criteria described above will be apparent to those skilled in the art.

Examples of low dose, low solubility active ingredients comprises of but not limited to fluvoxatine hydrochloride, sertraline, fluvoxatine maleate, alprazolam, candasartan

celexitil, clozapine, famotidine, carvedilol, diclofenac sodium, indapamide, etc.

Examples of low dose, high solubility active ingredients comprises of but not limited to captopril, ranitidine hydrochloride, lisinopril, tramadol, cerivastatin, methylphenidate hydrochloride, oxybutynin chloride, venlafaxine hydrochloride, alandronate sodium, metformin etc.

In the dosage form of the present invention, the outer portion may optionally contain more than one high dose low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient.

As indicated above the outer portion of the present invention may comprise auxiliary excipients such as for example lubricants, plasticisers, anti-tack agents, opacifying agents, pigments, and such like. As will be appreciated by those skilled in the art, the exact choice of excipient and their relative amounts will depend to some extent on the final oral dosage form.

Suitable lubricants, including agents that act on the flowability of the powder to be compressed are, for example, colloidal silicon dioxide such as Aerosil 200 (Aerosil is a Trade Mark); talc; stearic acid, magnesium stearate, calcium stearate and sodium stearyl fumarate.

In micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:1 to 100:75, more particularly from 100:2.5 to 100:50, still more preferably from100:2.5 to 100:30 and most preferably from 100:2.5 to 100:20.

In outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are preferably present in a ratio of from 100:0.5 to 100:75, more particularly from 100:2.5 to 100:50, still more preferably from100:2.5 to 100:30 and most preferably from 100:2.5 to 100:20.

According to one embodiment the release controlling agents are pharmaceutically excipients, which are hydrophobic in nature.

The polymers that can be used to form the rate-controlling membrane or micromatrix are described in greater detail herein below.

The hydrophobic release controlling agents are selected from but are not limited to Ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, Polyacrylate dispersion 30% as described in Ph. Eur., Polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), and poly (hexyl methacrylate), Poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite, fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol and myristyl alcohol, and fatty acid esters such as glyceryl monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, and hydrogenated castor oil.

According to an especially preferred embodiment the release controlling agents contains ammonio methacrylate co-polymers and fatty acid esters as hereinafter described.

The suitable hydrophobic agents are polymers sold under the Trade Mark Eudragit RS (Ammonio Methacrylate Copolymer type B USP), (Eudragit NE 30D (Polyacrylate dispersion 30% Ph. Eur.), Eudragit RL (Ammonio Methacrylate Copolymer type A USP) and Kollicoat SR 30 D and fatty acid esters such as glyceryl behenate, glycerol distearate and hydrogenated castor oil. Eudragit polymers are polymeric lacquer substances based on acrylate and/or methacrylates.

The outer portion can also include one or more commonly used excipients in oral pharmaceutical formulations.

Representative commonly used excipients in oral pharmaceutical formulations include talc, fumed silica, glyceryl monostearate, magnesium stearate, calcium stearate, kaolin, colloidal silica, gypsum, Tween 80, Geleol pastiles (trade mark), micronised silica and magnesium trisilicate.

The quantity of commonly used excipients in oral pharmaceutical formulations used is from about 0.5% to about 200% by weight, preferably from 2 to 100% more

particularly 10 to 60% based on the total dry weight of the polymer.

The outer portion can also include a material that improves the processing of the release controlling agents. Such materials are generally referred to as "plasticisers" and include, for example, adipates, azelates, benzoates, citrates, isoebucaes, phthalates, sebacates, stearates, tartrates, polyhydric alcohols and glycols.

Representative plasticisers include acetylated monoglycerides, butyl phthalyl butyl gylcolate, dibutyl tartrate, diethyl phthalate, dimethyl phthalate,, ethyl phthalyl ethyl glycolate, glycerin, ethylene glycol, propylene glycol, Triethyl citrate, triacetin, tripropinoin, diacetin, dibutyl phthalate, acetyl monoglyceride, polyethylene glycols, castor oil, triethyl citrate, polyhydric alcohols, acetate esters, glycerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisoctyl trimellitate, diethylexyl phthalate, di-n-octyl phthalate, di-I-octyl phthalate, di-I-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylexyl trimellitate, di-2-ethylexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, glyceryl monocaprylate, glycerol distearate and glyceryl monocaprate.

The amount of plasticiser to be used is from about 1% to 50% based on the weight of the dry release controlling agent(s).

The amount of release controlling agent(s) to be used in forming the outer portion will be determined based on various parameters such as the desired delivery properties, including the amount of active ingredient to be delivered, the active ingredient release rate desired, and the size of the micro matrix particles.

The novel dosage form of the present invention can be manufactured by the following procedure:

A) Inner Portion

The granules of the inner portion can be manufactured in accordance with usual techniques in which the active ingredient and other excipients are mixed and granulated by adding solution of binder in a low or high shear mixer or by fluidized bed granulation. The granulate is dried, preferably in a fluidized bed dryer. The dried granulate is sieved and mixed with lubricants and disintegrants.

Alternatively the manufacture of granules of inner portion can be made by direct mixing of the directly compressible excipients or by roller compaction.

B) Outer Portion

The micro matrix particles of the outer portion can be manufactured in accordance with usual techniques in which the active ingredient and one or more hydrophobic release controlling agents are mixed and granulated by adding solvent in a low or high shear mixer or by fluidized bed granulator. The granulate is dried, preferably in a fluidized bed dryer. The dried granulate is sized. The sizing of the micromatrix particles can be done using oscillating granulator, comminuting mill or any other conventional method. The sieve used for the sizing can have openings from 0.25 mm to 5 mm. Alternatively the micro matrix particles can be made by extrusion, spheronization or by roller compaction. The micro matrix particles can be coated by a solution of one or more hydrophobic release controlling agents by any known method, including spray application. Spraying can be carried out using a fluidized bed coated (preferably Wurster coating), or in a pan coating system. Alternatively the coating of the micro matrix particles with one or more rate controlling agents can be done by hot melt process using a granulator or fluidized bed coated (preferably Wurster coating), or in a pan coating system.

C) Tablet Compression

The compression of tablets is carried out on usual press coaters (e.g. machines of the Manesty, Cadmach or Kilian) with slight modification. The device such as feed frame and hoppers making top layer are eliminated. The granules of the inner layer are charged in the hopper of the machine compressing first layer and the granules of the outer layer are charged in the hopper of the machine compressing the coating. On operation only the bottom layer of the coating (outer portion) is deposited into the die and the first layer is placed on it. The compression wheels then embed the first layer in the granules of the outer layer, displacing some of latter to form sides, and finally press the whole into the tablet. The resultant tablet has inner portion covered by the outer portion from all the sides except top surface that remains uncovered and the level of the inner portion and the outer portion is same. The tablets can be made of various sizes and shapes. The present invention uses round punch tooling with upper flat bottom punches and lower flat bottom beveled edges lower

punches for the compression of inner portion and oblong shaped flat bottom beveled edges punches for the compression of the outer portion.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plan view of the dosage form described in the present invention,

FIG. 2 is an edge view of the dosage form described in the present invention,

FIG. 3 is a transverse section view as seen along the line 3-3 of Fig.1,

FIG. 4 (a) is a cross section of coated micro matrix particles prepared by spheronization and coating for the purpose of illustration only.

FIG. 4 (b) is a cross section of coated micro matrix particles prepared by granulation and coating for the purpose of illustration only.

Referring to FIGS. 1 to 3, a dosage form 4 as described in the present invention having an inner portion 1 containing low dose active ingredient as immediate release and outer portion 2 containing high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient as modified release. FIG. 4(a)& 4(b) shows the cross section of the coated micro matrix particles 5 and having 6 a high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient, 7 hydrophobic release controlling agent and 8 a coating of hydrophobic release controlling agent.

EXAMPLES

The following example further indicates but by no means limit the present invention.

1) Production of inner portion

Active ingredient	0.1	to 90	% w/w
Diluent(s)	10.0	to 90	% w/w
Binder	0.5	to 20	% w/w
Disintegrating agent	0.5	to 20	% w/w
Lubricant(s)/colourants	0.1	to 05	% w/w

Active ingredient is mixed with diluent(s) and the mixture is granulated with binder solution in appropriate

solvent(s) and then dried. The granules are sieved and mixed lubricants/colourants. This mixture is compressed to tablets of desired weight and punches.

2) Production of outer portion
A) Micro matrix particles-

The active ingredient and release controlling agent(s) are present in a ratio of from 100:1 to 100:75 %w/w

Active ingredient is mixed with release controlling agent(s) and the mixture is granulated with a suitable solvent(s) and then dried. The granules are sized.

B) Coating of Micro matrix particles-

Micro matrix particles and release controlling agent(s) for coating are present in a ratio of from 100:0.5 to 100:75 %w/w.

Micro matrix particles are charged in fluidized bed processor. Release controlling agent(s) is/are dissolved in suitable solvent and this coating solution is sprayed to coat the micro matrix particles. The coated micro matrix particles are sieved and mixed with lubricants.

3) Compression of tablets
Tablet- Granules of inner portion are pressed to tablets of smaller dimention and granules of outer portion compressed on punches of higher dimention.

The compression is done on press coater machine in such a manner that the resultant tablet has inner portion covered by the outer portion from all the sides except top surface that remains uncovered and the level of the inner portion and the outer portion is on the same surface.

Example - 1

Manufacturing process is divided into three parts.
Part 1: Manufacturing of Metformin Hydrochloride Sustained Release Fraction.
Part 2: Manufacturing of Nebivolol Hydrochloride Fraction.
Part 3: Compression of tablets using Part 1 and Part 2.

Part 1: Manufacturing of Metformin Hydrochloride Sustained Release Fraction.

Sr. No.	Ingredients	Qty / Tab (mg)	% w/w	Qty / Tab (mg)	% w/w
		For 250 mg		For 375 mg	
Preparation of Metformin HCl Granules:					
1	Metformin Hydrochloride	250	72.0	375	72.0
2	Ammonio methacrylate copolymer, Type B	50	14.4	75	14.4
Coating of Metformin HCl Granules:					
3	Castor oil, hydrogenated (Cutina HR PH)	43.75	12.6	65.625	12.6
Lubrication:					
4	Magnesium stearate	3.25	0.9	4.875	0.9

Procedure:

A) Stage I- Granulation

Milling:

Mill Metformin HCl through 0.5 mm screen.

Sifting:

Sift milled Metformin HCl, Eudragit RSPO through # 40 mesh.

Granulation:

Premixing - Mix the material of step 2 in granulator
Binder addition - Add Methylene chloride and Acetone (1:1) into the premix blend.
Wet mixing - Knead the above mixture for sufficient period to get the granules of uniform consistency.

Drying:

Dry the granules in Dryer till LOD reaches below 1%.

Sizing:

Size the granules through 1 mm sieve in oscillating granulator.

Stage II - Coating Of Granules

1) Prepare Cutina solution by dissolving Castor Oil, hydrogenated (Cutina PH HR) in methylene chloride.
2) Coat the sized Metformin granules (Stage I) with the Castor Oil, hydrogenated (Cutina PH HR) solution in Fluid bed processor.
3) Sift the coated Metformin granules through # 16.

Stage III - Lubrication

1) Lubricate the coated granules (Stage II) with Magnesium stearate previously passed through # 60.

Part 2: Manufacturing of Nebivolol Hydrochloride Fraction.

Sr. No.	Ingredients	Qty / Tab (mg)	% w/w
Intragranular			
1	Nebivolol Hydrochloride	5.45	6.1
2	Lactose monohydrate	65.05	72.3
3	Croscaramolose Sodium	5.00	5.6
4	Ferric Oxide Red	1.00	1.1
5	Polyvinyl Pyrrolidone K-30	3.00	3.3
Extragranular			
6	Croscaramolose Sodium	9.00	10.0
7	Colloidal Silicon Dioxide	0.50	0.6
8	Magnesium Stearate	1.00	1.1

Procedure:

A) Stage I- Granulation

1) Sifting:

Sift Nebivolol hydrochloride, Lactose monohydrate, and Croscaramallose sodium through # 40 mesh.
Sift Ferric oxide red through # 100 mesh.

2) Granulation:

Premixing – Mix the material of step 1 in granulator.

Preparation of binding solution: Dissolve Polyvinyl Pyrrolidone K-30 in sufficient quantity of Purified water.

Binder addition – Add the binding solution into the premix blend.

Wet mixing – Knead the above mixture for sufficient period to get the granules of uniform consistency. Add extra purified water if needed.

3) Drying:

Dry the granules in Dryer till LOD reaches between 1.4-2.0 %.

4) Sizing:

Size the granules through # 20 mesh.

B) Stage II – Lubrication:

Sift Croscaramolose sodium, Colloidal silicon dioxide through # 40 mesh and mix with the sized granules. Lubricate the granules with Magnesium stearate previously sifted through # 60 mesh.

Part 3: Compression of tablets using Part 1 and Part 2 Fractions.

Sr. No.	Fraction	Weight / Tablet (in mg)	
		For 250 + 5 mg	For 375 + 5 mg
1	Metformin hydrochloride sustained release fraction (Part 1)	347	520.5
2	Nebivolol hydrochloride fraction (Part 2)	90	90
3	Total Weight	437	610.5

Method for compression:

For 250 + 5 mg:
Compress inlay tablets as per the weights given in part 3 using appropriate tooling on tablet press.

For 375 +5 mg:

Compress inlay tablets as per the weights given in part 3 using appropriate tooling on tablet press.

DISSOLUTION:

For Metformin HCl:
USP Apparatus II (Paddle), RPM- 50, Medium-0.1 N HCL, Medium- 900 ml.

Time Points (hr)	250 + 5 mg % Drug release	375 + 5 mg % Drug release
1	39.62	31.54
2	57.16	43.98
4	80.37	63.80
6	94.85	77.28
8	99.59	87.33
10	104.08	94.75
12	105.03	99.25

For Nebivolol:

USP Apparatus II (Paddle), RPM- 100, Medium-0.1 N HCL, Medium- 500 ml.

Time Points (min)	250 + 5 mg % Drug release	375 + 5 mg % Drug release
15	60.0	59.3
30	67.6	66.4
45	69.1	68.8
60	69.9	70.6
90	71.5	72.2

Example - 2

Manufacturing process is divided into three parts.
Part 1: Manufacturing of Metformin Hydrochloride Sustained Release Fraction.
Part 2: Manufacturing of Nebivolol Hydrochloride Fraction.
Part 3: Compression of tablets using Part 1 and Part 2.

Part 1: Manufacturing of Metformin Hydrochloride Sustained Release Fraction.

Sr. No.	Ingredients	Qty / Tab (mg)	% w/w
Preparation of Metformin HCl Granules:			
1	Metformin Hydrochloride	250	72.0
2	Ammonio methacrylate copolymer, Type B	50	14.4
Coating of Metformin HCl Granules:			
3	Castor oil, hydrogenated (Cutina HR PH)	43.75	12.6
Lubrication:			
4	Magnesium stearate	3.25	0.9

Procedure:

A) Stage I- Granulation

Milling:
Mill Metformin HCl through 0.5 mm screen.

Sifting:
Sift milled Metformin HCl, Eudragit RSPO through # 40 mesh.

Granulation:

Premixing - Mix the material of step 2 in granulator
Binder addition - Add Methylene chloride and Acetone (1:1) into the premix blend.
Wet mixing - Knead the above mixture for sufficient period to get the granules of uniform consistency.

Drying:
Dry the granules in Dryer till LOD reaches below 1%.

Sizing:
Size the granules through 1 mm sieve in oscillating granulator.

Stage II - Coating Of Granules

4) Prepare Cutina solution by dissolving Castor Oil, hydrogenated (Cutina PH HR) in methylene chloride.
5) Coat the sized Metformin granules (Stage I) with the Castor Oil, hydrogenated (Cutina PH HR) solution in Fluid bed processor.
6) Sift the coated Metformin granules through # 16.

Stage III - Lubrication

2) Lubricate the coated granules (Stage II) with Magnesium stearate previously passed through # 60.

Part 2: Manufacturing of Nebivolol Hydrochloride Fraction.

Sr. No.	Ingredients	Qty / Tab (mg)	% w/w
Intragranular			
1	Nebivolol Hydrochloride	5.45	6.1
2	Lactose monohydrate	70.63	78.5
3	Ferric Oxide Red	0.50	0.6
4	Polyvinyl Pyrrolidone K-30	3.00	3.3
Extragranular			
5	Polyplasdone XL-10	9.00	10.0
6	Colloidal Silicon Dioxide	0.50	0.6
7	Magnesium Stearate	0.90	1.0

Procedure:

A) Stage I- Granulation

1) Sifting:
Sift Nebivolol hydrochloride, Lactose monohydrate through # 40 mesh.
Sift Ferric oxide red through # 100 mesh.

2) Granulation:
Premixing - Mix the material of step 1 in granulator.

Preparation of binding solution: Dissolve Polyvinyl Pyrrolidone K-30 in sufficient quantity of Purified water.

Binder addition - Add the binding solution into the premix blend.

Wet mixing - Knead the above mixture for sufficient period to get the granules of uniform consistency. Add extra purified water if needed.

3) Drying:
Dry the granules in Dryer till LOD reaches between 1.4-2.0 %.

4) Sizing:
Size the granules through # 20 mesh.

B) Stage II - Lubrication:

Sift Polyplasdone XL-10, Colloidal silicon dioxide through # 40 mesh and mix with the sized granules.
Lubricate the granules with Magnesium stearate previously sifted through # 60 mesh.

Part 3: Compression of tablets using Part 1 and Part 2 Fractions.

Sr. No.	Fraction	Weight / Tablet (in mg)
		For 250 + 5 mg
1	Metformin hydrochloride sustained release fraction (Part 1)	347
2	Nebivolol hydrochloride fraction (Part 2)	90
3	Total Weight	437

Method for compression:

Compress inlay tablets as per the weights given in part 3 using appropriate tooling on tablet press.

DISSOLUTION:

For Metformin HCl:
USP Apparatus II (Paddle), RPM- 50, Medium-0.1 N HCL, Medium- 900 ml.

Time Points (hr)	250 + 5 mg
	% Drug release
1	37.87
2	54.34
4	79.60
6	95.04
8	103.03

For Nebivolol:
USP Apparatus II (Paddle), RPM- 100, Medium-0.1 N HCL, Medium- 500 ml.

Time Points (min)	250 + 5 mg % Drug release
15	61.1
30	72.8
45	78.6
60	87.1
90	92.9

What is claimed is:

1.A combination dosage form of -

i) high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose, high solubility active ingredient, as modified release and

ii) low dose active ingredient as immediate release,

wherein the said dosage form comprises of an inner portion having a low dose active ingredient as immediate release and an outer portion having a high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose, high solubility active ingredient as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix particles.

2. A dosage form of combination of low dose, high solubility active ingredient metformin, as modified release and low dose active ingredient nebivolol as immediate release, wherein said dosage form comprises of an inner portion having a low dose active ingredient nebivolol as immediate release and an outer portion having a low dose, high solubility active ingredient metformin as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix particles.

3. A dosage form according to claim 1 and 2, in the form of a tablet, wherein said inner portion is covered by the outer portion from all the sides except top surface that remains uncovered.

4. A dosage form according to claim 1 and 2, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.

5. A dosage form according to claim 1 and 2, wherein the micro matrix particles comprises one or more hydrophobic release controlling agents.

6. A dosage form according to claim 5, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher

molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate), poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite, fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol and myristyl alcohol, and fatty acid esters such as glyceryl monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate and hydrogenated castor oil.

7. A dosage form according to claim 6, wherein the hydrophobic release controlling agent(s) is selected preferably from ammonio methacrylate co-polymers.

8. A dosage form according to claim 7, wherein the preferred ammonio methacrylate co-polymers are selected from Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP), Eudragit RL (Ammonio Methacrylate Copolymer type A USP) and Eudragit NE30D (Polyacrylate dispersion 30% Ph. Eur.).

9. A dosage form according to claim 1 and 2, wherein in micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are present in a ratio of from 100:1 to 100:75.

10. A dosage form according to claim 1 and 2, coating of micro matrix particles comprises one or more hydrophobic release controlling agents.

11. A dosage form according to claim 10, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate),

poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite, fatty alcohols such as cetostearyl alcohol, stearyl alcohol, cetyl alcohol and myristyl alcohol and fatty acid esters such as glyceryl monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate glycerol distearate, and hydrogenated castor oil.

12. A dosage form according to claim 11, wherein the hydrophobic release controlling agent(s) is selected from fatty acid esters.

13. A dosage form according to claim 12, wherein the hydrophobic release controlling agents is selected from the group comprising of hydrogenated castor oil and glycerol distearate.

14. A dosage form according to claim 1 and 2, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present in a ratio of from 100:0.5 to 100:75.

15. A dosage form according to claim 1 and 2, wherein the weight ratio of immediate release active ingredient and modified release active ingredient with high dose, low solubility is from 1:10 to 1:15000.

16. A dosage form according to claim 1 and 2, wherein the weight ratio of immediate release active ingredient and modified release active ingredient with low dose is from 500:1 to 1:5000.

17. A dosage form according to claim 1 and 2, wherein the low dose active ingredient for immediate release comprises dose less than or equal to 50 mg.

18. A dosage form according to claim 1 and 2, wherein the low dose active ingredient for immediate release is selected from the group comprising of antidiabetic agents, anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arthritics, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme

inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors, vertigo agents, sulphonylurease, meglitinides, PPAR gamma agonist [insulin sensitisers (thiazolidinedione)], PPAR alpha and gamma agonist, alpha-glucosidase inhibitors and the like.

19. A dosage form according to claim 18, wherein the low dose active ingredient for immediate release is selected from the group comprising of zafirlukast, quinapril hydrochloride, isotretinoin, rabeprazole sodium, estradiol(e2), norethindrone acetate, risedronate sodium, pioglitazone HCl, amphetamine, anagrelide hydrochloride, biperiden HCl, mephalan, alprazolam, ramipril, naratriptan hydrochloride, leflunomide, anastrozole, exemestane, paroxetine mesylate, candesartan cilexetil, almotriptan, cerivastatin, betaxolol hydrochloride, bisoprolol fumarate, deloratadine, clonazepam, clorazepate dipotassium, clozapine, methylphenidate HCl, carvedilol, warfarin sodium, norgestrel, ethinyl estradiol, cyclophosphamide, pemoline, liothyronine sodium, misoprostol, tolterodine tartrate, dextroamphetamine sulfate, dicyclomine hydrochloride, digoxin, oxybutynin chloride, doxazosin mesylate, ethacrynate sodium, venlafaxine HCl, enalapril maleate, estradiol, estropipate, famotidine, letrozole, fludrocortisone acetate, fluoxetine, dexmethylphenidate HCl, alendronate sodium, ziprasidone, glipizide, glyburide, miglitol, guanabenz acetate, haloperidol, doxercalciferol, zalcitabine, hydrochlorothiazide, hydromorphone HCl, indapamide, estradiol, nitric oxide, ketorolac tromethamine, clonazepam, granisetron, lamotrigine, fluvastatin sodium, levonorgestrel, levothyroxine sodium, atorvastatin calcium, lisinopril, minoxidil, loperamide, loratidine, lorazepam, lovastatin, pravastatin sodium, fluvoxamine maleate,

acetaminophen, acyclovir, aminocaproic acid, pitavastatin, rosuvastatin, dalvastatin, escetalopram, sertraline, celecoxib, parecoxib, valdecoxib, glibenclamide (glyburide), glipizide, gliclazide, glimepiride, tolazamide, tolbutamide, clorpropamide, gliquidone, nateglinide, glyburide, glisoxepid, glibornuride, phenbutamide, tolcyclamide, repaglinide, troglitazone, ciglitazone, pioglitazone, englitazone, acarbose, voglibose, emiglitate, miglitol, farglitazar, nebivolol, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl]propanoic acid, 3-{4-[2-(4-tert-butoxy-carbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, L-6766892 and pharmaceutically acceptable salts thereof.

20. A dosage form according to claim 1 and 2, wherein the high dose, low solubility active ingredient for modified release comprises dose from 500 mg to 1500 mg.

21. A dosage form according to claim 1 and 2, wherein the low dose active ingredient for modified release comprises dose from 0.1 mg to 500 mg.

22. A dosage form according to claim 1 and 2, wherein the high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose, high solubility active ingredient is selected from the group comprising of antidiabetic agents, anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arththriics, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal

preparations, vaso-constrictors, biguanides, vertigo agents and the like.

23. A dosage form according to claim 1 and 2, wherein high dose, low solubility active ingredients are selected form the group comprising of cefuroxime axetil, acetylsalicyclic acid, ibuprofen, gemfibrozil, sulfasalazine, acyclovir, cefadroxil, amoxicillin, cefaclor, ticlopidine hydrochloride, ciprofloxacin hydrochloride and pharmaceutically acceptable salts thereof.

24. A dosage form according to claim 1 and 2, wherein low dose, low solubility active ingredients are selected form the group comprising of fluvoxatine hydrochloride, sertraline, fluvoxatine maleate, alprazolam, candasartan celexitil, clozapine, famotidine, carvedilol, diclofenac sodium, indapamide and pharmaceutically acceptable salts thereof.

25. A dosage form according to claim 1 and 2, wherein low dose, high solubility active ingredients are selected form the group comprising of captopril, ranitidine hydrochloride, lisinopril, tramadol, cerivastatin, methylphenindate hydrochloride, oxybutynin chloride, venlafaxine hydrochloride, alandronate sodium, metformin and pharmaceutically acceptable salts thereof.

26. A dosage form according to claim 1 and 2, wherein inner portion may optionally contain more than one low dose active ingredients for immediate release.

27. A dosage form according to claim 1 and 2, wherein the dosage form can be given twice a day or more preferably can be given once a day oral formulation.

28. A dosage form according to claim 1 and 2, is used for human beings.

29. A process for the preparation of a dosage form comprising a) preparation of inner portion and b) preparation of outer portion.

30. A process for the preparation of a dosage form as claimed in claim 29, wherein preparation of outer portion comprising a) preparing a micro matrix particles containing high dose, low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredient and one or more hydrophobic release controlling agent and b) coating the said micro matrix particles containing active ingredient and one or more hydrophobic release controlling agent.

31. A dosage form according to claim 1 and 2, wherein outer portion may optionally contain more than one high dose low solubility active ingredient or low dose, low solubility active ingredient or low dose high solubility active ingredients.

32. A dosage form as defined herein, substantially described particularly with reference to the foregoing example.

FIGURE 1

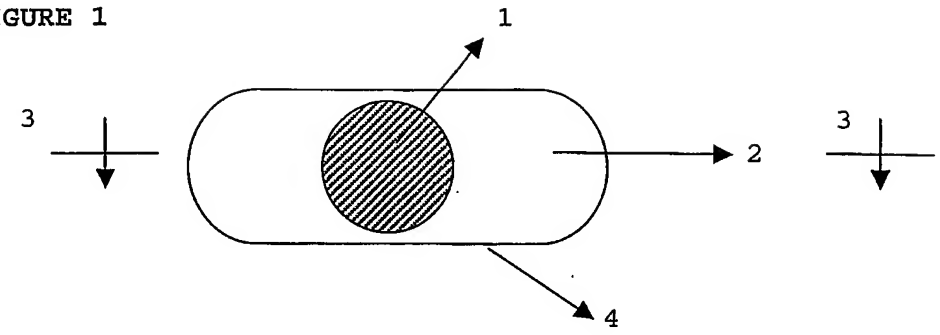


FIGURE 2

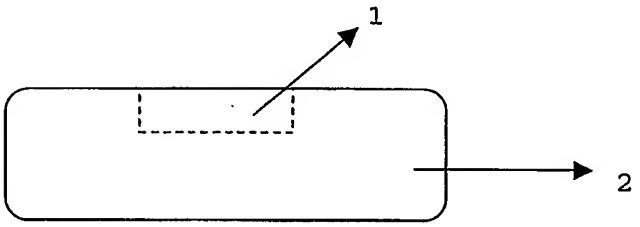


FIGURE 3

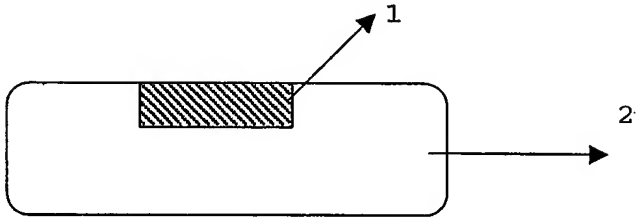


FIGURE 4(a)

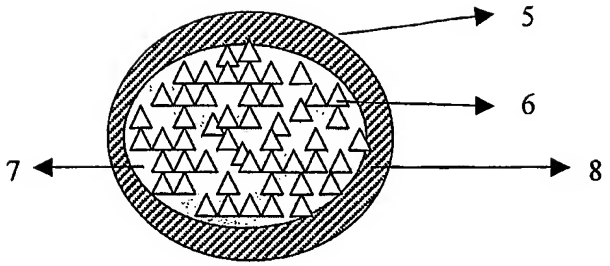
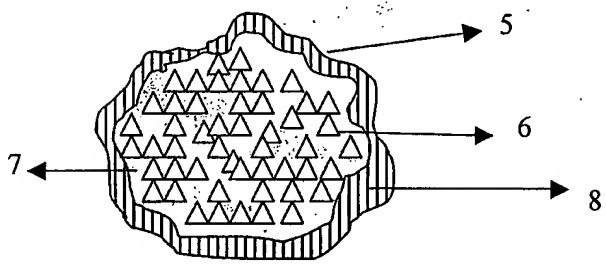


FIGURE 4(b)



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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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(54) Title: NOVEL PHARMACEUTICAL COMPOSITIONS

(57) Abstract: A dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release. Wherein the modified release active ingredient is selected from high dose, low solubility active ingredients or low dose, low solubility active ingredients or low dose, high solubility active ingredients and the immediate release active ingredient is selected from low dose active ingredients.

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 888 038 A (WILLIAM WARREN TRIGGS, C.B.E) 24 January 1962 (1962-01-24)	1,3-5, 10-12, 15, 17-19, 21,22, 26-32
A	page 2, lines 37-41 page 2, lines 50-64 page 2, line 121 - page 3, line 17 page 3, line 63 - line 71; examples I-III page 4, lines 66-70; claim 1	2,6-9, 13,14, 16,20, 23-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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29 June 2005	08/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 00/40233 A (HEXAL AG; STRUENGMANN, THOMAS) 13 July 2000 (2000-07-13) page 4, line 12 - page 5, line 20; claims 10,12,14-19	1-32

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